



Atty. Dkt. No. 029318-0104

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Elaine LIVERSIDGE et al.
Title: ***STABILIZATION OF CHEMICAL COMPOUNDS
USING NANOPARTICULATE FORMULATIONS***
Appl. No.: 09/952,032
Filing Date: 09/14/2001
Examiner: M. P. Young
Art Unit: 1615

DECLARATION UNDER 37 CFR § 1.132

I, H. William Bosch, hereby declare that:

1. I received my Ph.D. degree in 1987 from The University of Pennsylvania in Chemistry. I have been working in the field of nanoparticulate drug technology since 1991, when I joined Sterling Winthrop Pharmaceuticals Research Division.

2. The portion of Sterling Winthrop Pharmaceuticals Research Division involved in nanoparticulate drug technology was sold and became known as NanoSystems. This business was then sold and became known as Elan Drug Delivery.

3. Currently I am the Director of Dispersion Technology at Elan Drug Delivery, with offices at 3500 Horizon Drive, King of Prussia, PA 19406.

4. I have reviewed and understood the subject patent application. I have also read and understood the non-final Office Action dated October 22, 2003, together with the references cited therein.

5. In response to the specific points raised in the Examiner Interview, dated January 14, 2004, I present two references that document how surface stabilizers in a nanoparticulate active agent composition behave not as impenetrable shells, but rather as permeable layers allowing ingress and egress of environmental conditions.

6. In response to the specific points raised in the Examiner Interview, I also present experimental data showing, contrary to conventional wisdom, the unexpected stability of

nanoparticulate active agent compositions, notwithstanding the access of environmental conditions to the drug particles themselves.

7. Practitioners who are skilled in the nanoparticulate active agent formulation art universally accept the fact that surface stabilizers, when adsorbed to the surface of a drug nanoparticle, do not form impenetrable shells about the drug nanoparticle. Rather, the surface stabilizers engender a *permeable* layer that permits solvent molecules, for example, access to the nanoparticulate compound itself.

a. See G. P. van der Beek et al., "Polymer Adsorption and Desorption Studies via ^1H NMR Relaxation of the Solvent," *Langmuir*, 7:327-334 (1991) (Exhibit 1). This reference examines the theoretical and experimental underpinnings of proton relaxation in water as a function of water in the bulk versus water that is present at the surface of silica nanoparticles. "The essential features of the observed relaxation behavior can be understood by means of rapid exchange between solvent molecules at the silica surface with a short relaxation time T_{ib} and free molecules in the bulk with a longer relaxation time T_{if} ." *Id.* at page 328, col. 1. Thus, notwithstanding the presence of adsorbed surface stabilizers such as polyethylene glycol and polyvinylpyrrolidone (*id.* at page 329, col. 1), water can and does interact with the nanoparticulate silica.

b. See T. Cosgrove et al., "Solvent relaxation NMR: bound fraction determination for sodium poly(styrene sulphonate) at the solid/solution interface," *Colloids and Surfaces*, 64:311-316 (1992) (Exhibit 2). This reference, as with van der Beek et al. discussed above, bolsters the view that surface stabilizers that are adsorbed to a nanoparticulate compound, here polystyrene latex, form a *permeable* layer on the surface of the nanoparticulate compound. This study, however, employed the strongly hydrophobic surface stabilizer sodium poly(styrene sulphonate), which was understood to prevent easy ingress of water molecules. See Cosgrove et al. at page 315, col. 1. The hydrophobic surface stabilizer layer notwithstanding, "[i]t appears that there is still some solvent interaction with the particle." *Id.*

8. Light is another example of an environmental condition that penetrates layers of adsorbed surface stabilizers. Notwithstanding the direct access of light to drug nanoparticles, the nanoparticulate drug compositions do not decompose.

a. In one experiment, separate volumes of: (1) pure fluorescein diacetate and (2) a nanocrystalline colloidal dispersion of fluorescein diacetate were exposed to visible light:

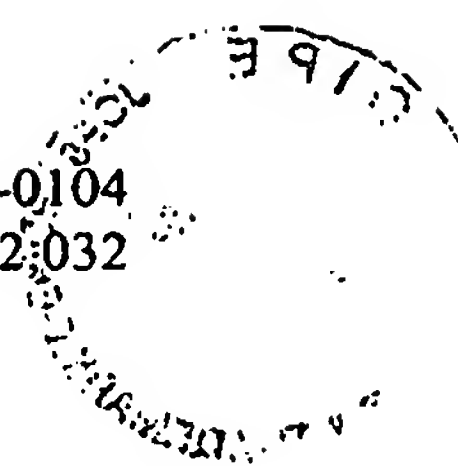
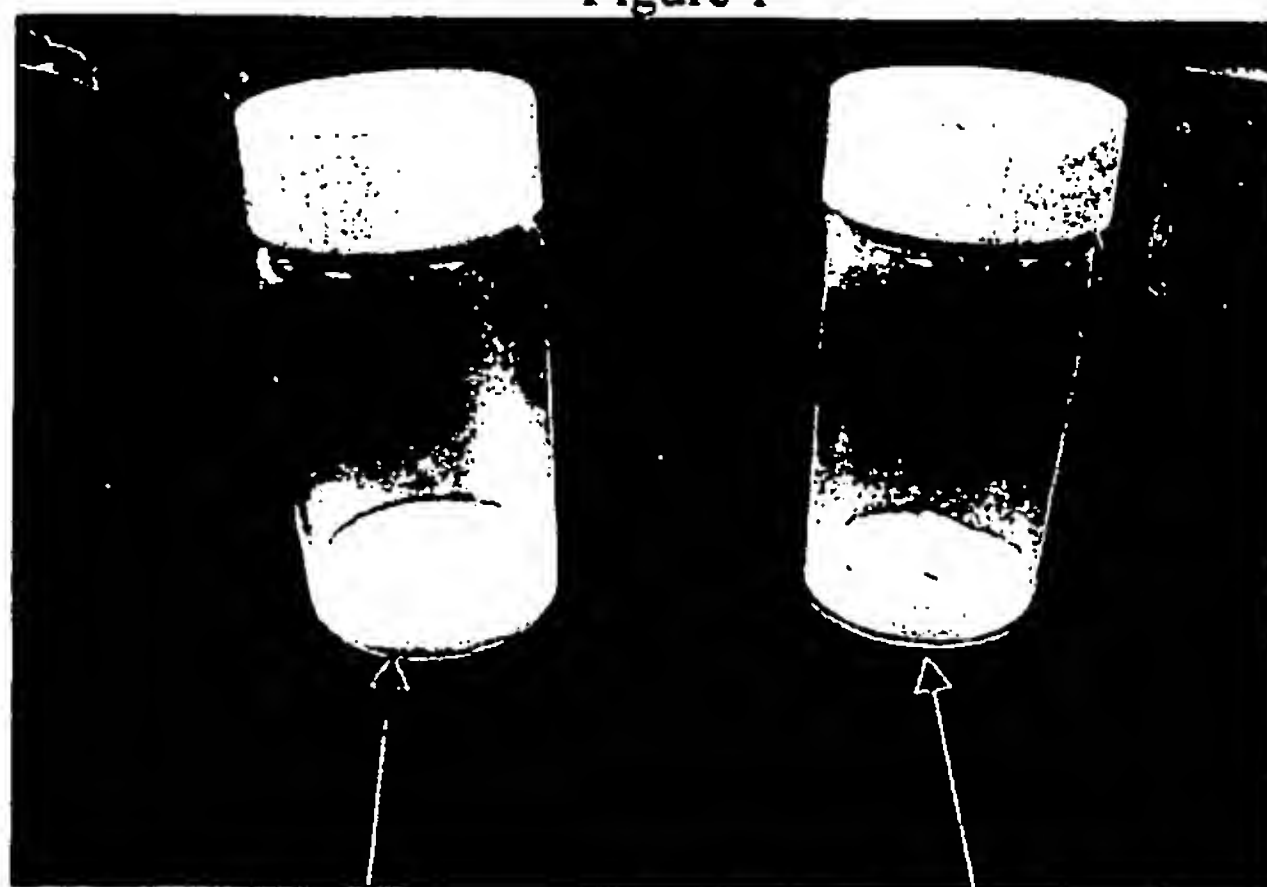


Figure 1

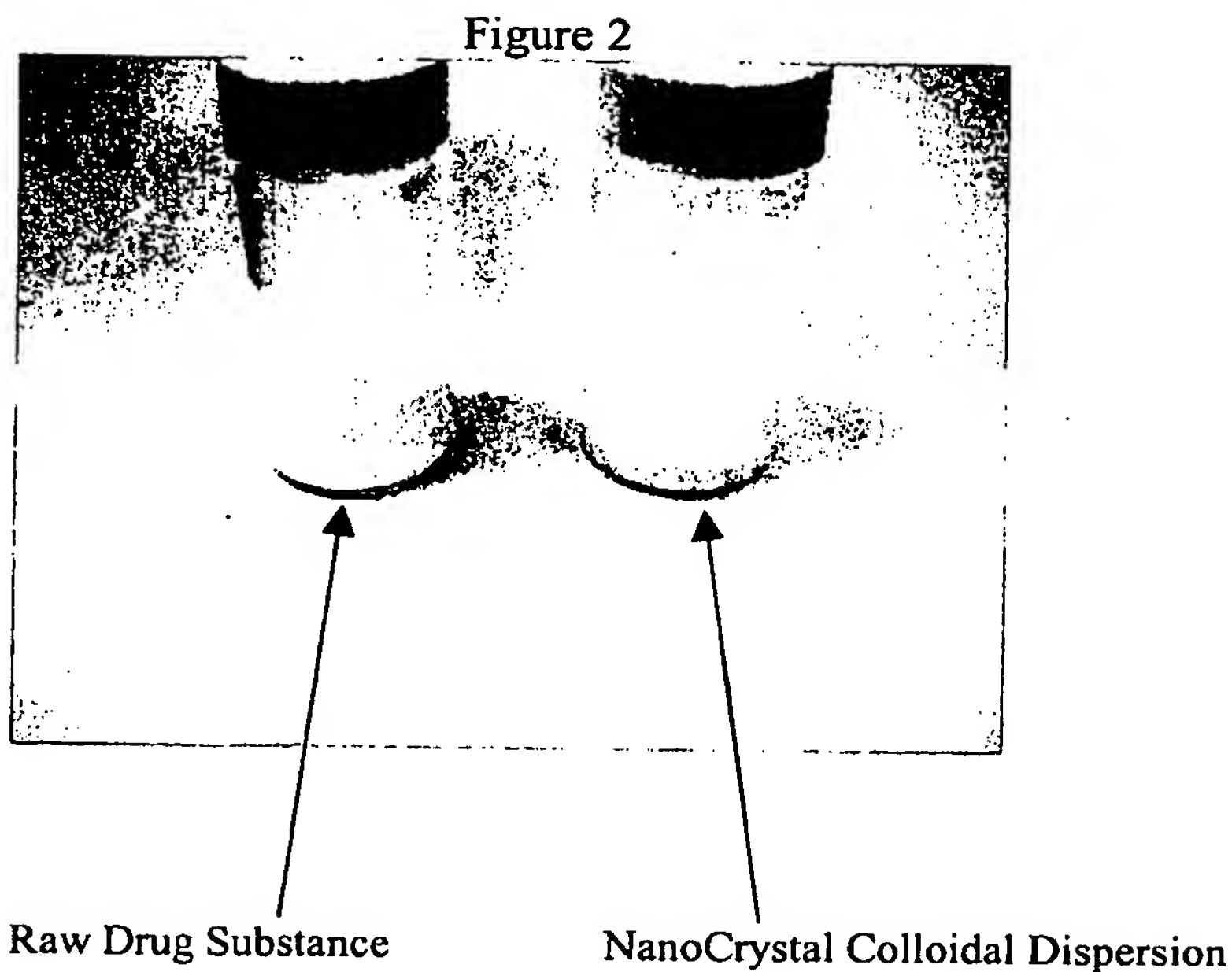


NanoCrystal Colloidal Dispersion

Raw Drug Substance

As shown in Figure 1 above, the colors of pure fluorescein diacetate and the corresponding nanoparticulate fluorescein diacetate composition are each white, thus demonstrating that light penetrates the adsorbed layer of surface stabilizer.

b. In an analogous experiment, separate volumes of: (1) nifedipine and (2) a nanocrystalline colloidal dispersion of nifedipine each gave rise to a yellow color when exposed to visible light:



The data presented in Figure 2 represents additional proof that light freely penetrates the surface stabilizer layer, and thereby accesses the surface of the nanoparticulate drug.

9. Conventional understanding in the art and the experimental results outlined above therefore demonstrate how adsorbed surface stabilizers do not form impenetrable shells about a nanoparticulate compound, but rather freely allow interaction of environmental conditions with the nanoparticulate compound.

10. The experimental results additionally show that nanoparticulate active agent compositions maintain their *chemical* stability despite this *physical* form of compounds presenting very large surface area relative to its volume.

11. I declare that the statements made herein of my knowledge are true and all statements on information and belief are believed to be true; and further these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing therein.

H. William Bosch
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March 11, 2004
Date